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Helminths and Immunological Tolerance

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and Rick M. Maizels^{1,3}

Current immunosuppression regimens for solid-organ transplantation have shown disappointing efficacy in the prevention of chronic allograft rejection and carry unacceptable risks including toxicity, neoplasia, and life-threatening infection. Achievement of immunological tolerance (long-term antigen unresponsiveness in an immunocompetent host) presents the exciting prospect of freedom from immunosuppression for transplant recipients. It is now 60 years since the first demonstration of immunological tolerance in animal models of transplantation, but translation into routine clinical practice remains elusive. Helminth parasites may provide novel strategies toward achieving this goal. Helminths are remarkably successful parasites: they currently infect more than one quarter of the world's population. It is now well established that the parasites' success is the result of active immunomodulation of their hosts' immune response. Although this primarily secures ongoing survival of the parasites, helminth-induced immunomodulation can also have a number of benefits for the host. Significant reductions in the prevalence of allergy and autoimmune conditions among helminth-infected populations are well recognized and there is now a significant body of evidence to suggest that harmful immune responses to alloantigens may be abrogated as well. Here, we review all existing studies of helminth infection and transplantation, explore the mechanisms involved, and discuss possible avenues for future translation to clinical practice.

Keywords: Allograft tolerance, Allograft rejection, Helminth.

(*Transplantation* 2014;97: 127–132)

Successful organ transplantation requires negotiation of a number of complex immunologic barriers. In addition to cell-mediated rejection resulting from mismatching of major and minor histocompatibility complexes (1), innate immune responses are invariably stimulated by a combination of surgery itself and organ damage resulting from ischemia and reperfusion (2). Ever-increasing demand for organ transplantation has unfortunately coincided with a

steady decline in the availability of donor organs in recent decades (3). This has necessitated amended strategies to expand the donor pool that can result in donor organs of a lesser quality and/or greater degrees of immunologic mismatch (3).

Despite this, solid-organ transplantation has become the standard of care for numerous disease processes that result in organ failure. Advances in surgical techniques and immunosuppressive regimens mean that excellent short-term to medium-term graft survival has now come to be expected. However, recent scrutiny of long-term allograft survival data reveals that considerable improvements in the incidence and management of acute rejection have not been reflected in improved long-term outcomes (4). For living-donor kidney transplant recipients in the United States, organ graft survival half-life is almost unchanged (in 2005, this was 11.9 years compared with 11.4 years in 1989) (5). A similar disparity in short-term and long-term survival rates has also been seen in liver, lung, heart, intestine, and pancreas transplantation (6).

Current immunosuppression regimens used in solid-organ transplantation carry significant risks of toxicity, infection (7), and neoplasia (8). The incidence of neoplastic disorders such as posttransplantation lymphoproliferative disease, in particular, relates more to the intensity of immunosuppression than the specific agent used (1). All of these factors have fuelled the long-held ambition for allograft tolerance, defined as durable antigen-specific unresponsiveness in an immunocompetent host (9).

Despite the achievement of experimental murine allograft tolerance 60 years ago (10), translation to the clinical

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TABLE 1. Published studies reporting prolonged allograft survival in humans or laboratory animals in helminth-infected hosts, or in animals given helminth-derived products.

Authors	Parasite	Allograft model	Graft prolongation	P
Aboul-Enein et al. (41)	<i>Schistosoma mansoni</i>	Human skin	2.21	0.001
Hepiretihan et al. (32)	<i>Echinococcus multilocularis</i>	Rat heart	2.04	<0.05
Li et al. (31)	<i>E. multilocularis</i>	Rat liver	1.57	<0.05
Liwski et al. (34)	<i>Nippostrongylus brasiliensis</i>	Mouse heart	2.80	<0.03
Ledingham et al. (33)	<i>N. brasiliensis</i>	Rat kidney	3.30	<0.001
Araujo et al. (42)	<i>Nippostrongylus</i> NES	Rat kidney	2.22	<0.001
	<i>S. mansoni</i>	Mouse skin	1.5	<0.001
Svet-Moldavsky et al. (43)	<i>Trichinella spiralis</i>	Mouse skin	2.13	
Faubert and Tanner (44)	<i>T. spiralis</i>	Mouse skin	1.89	<0.001
Chimyskhan et al. (45)	Infected mouse serum	Mouse skin	1.67	
	<i>T. spiralis</i>	Mouse skin	2.48	<0.001
Alkarmi et al. (46)	<i>Trichinella pseudospiralis</i>	Mouse skin	3.57	—
	<i>T. pseudospiralis</i> extract	Mouse skin	2.0	—
	<i>T. spiralis</i>	Mouse skin	3.57	—
	<i>T. spiralis</i> extract	Mouse skin	2.43	—

setting has been frustratingly slow. Recent developments in the understanding of regulatory cell populations have, however, allowed some ground for optimism (11). In particular, a recent trial of combining kidney transplantation with a simultaneous bone marrow transplant from single human leukocyte antigen (HLA)–mismatched donors has allowed for successful withdrawal of all immunosuppression in four of five patients (12). With this technique, patients developed transient mixed chimerism and lasting specific alloantigen unresponsiveness as a result. With the same technique, Scandling et al. have independently demonstrated similarly impressive outcomes with HLA-matched kidney transplantation: from a cohort of 16 patients, 8 have achieved rejection-free avoidance of immunosuppressive medication for more than 1 year, and a further 4 patients are in the process of withdrawal from medication (13). Although many would consider simultaneous bone marrow transplantation to present an unacceptable level of complexity and risk in the pursuit of solid-organ allograft tolerance (9), this important study has shown lasting intragraft regulatory cell populations and the successful allograft tolerance this can achieve in a clinical setting.

The ability of regulatory T cells (Treg) to mediate allograft tolerance in murine models is now well recognized (14). Expectations of successful translation of Treg therapy into the clinical setting have been high and preliminary clinical trials have now been completed in graft-versus-host disease (15) and hematopoietic stem cell transplantation (16) with modest but encouraging results. However, a number of obstacles and concerns persist. First, Good Manufacturing Practice-compliant ex vivo expansion of Tregs for subsequent reinfusion is a highly specialized process at a cost of approximately \$40,000 per patient (17). Second, difficulty in identifying regulatory cell populations for purification and ensuring that they do not convert away from the regulatory phenotype presents the possibility of harm caused by inadvertent infusion of expanded effector T-cell populations (resulting in enhanced rejection or autoimmunity) (18). Finally, the specificity of Treg-induced immunosuppression is uncertain and may

therefore present a risk of infection or neoplasia similar to that of current global immunosuppression regimens. Although results from early studies provide some degree of reassurance in this regard (19), analysis of long-term clinical safety data is still awaited.

Helminth Infections and Host Immunity

Helminth worms are particularly successful parasites; as recently as 1940, the prevalence of infection in children in some rural areas of the United States was as high as 70% (20) and the current rate of chronic infection stands at more than one quarter of the world's population (21). Helminths' success is now recognized to be the result of active modulation of their hosts' immune response (21). In addition to facilitating chronic infection, parasite-derived dampening of the host systemic immune response also results in reduced reactivity to unrelated "bystander" allergens and autoantigens or alloantigens. In many cases, this effect is of some considerable benefit to the host. Recent studies have shown abrogation of multiple disease processes in the presence of helminth infection, including allergic airway inflammation, encephalitis, inflammatory bowel disease, rheumatoid arthritis, and type 1 diabetes in experimental models (22). Epidemiologically, it is well established that the prevalence of allergic and autoimmune disorders is higher in developed countries compared with developing nations. Recent cohort studies investigating allergic responses in children demonstrated reduced skin responses to antigen testing in helminth-infected subjects compared with controls and found that this effect was eliminated after clearance of infections with antihelminthic therapy (22). Similarly, patients with multiple sclerosis in Argentina who adventitiously acquired helminth infections were found to stay in remission but relapsed after antihelminthic drug treatment (23). A recent phase I trial of experimental helminth infection with *Trichuris suis* as a therapy for Crohn's disease revealed no adverse effects (in 29 patients) and showed promising considerable reductions in disease severity scores (24). Large-scale Good Manufacturing Practice-compliant production of *T. suis* for clinical use has

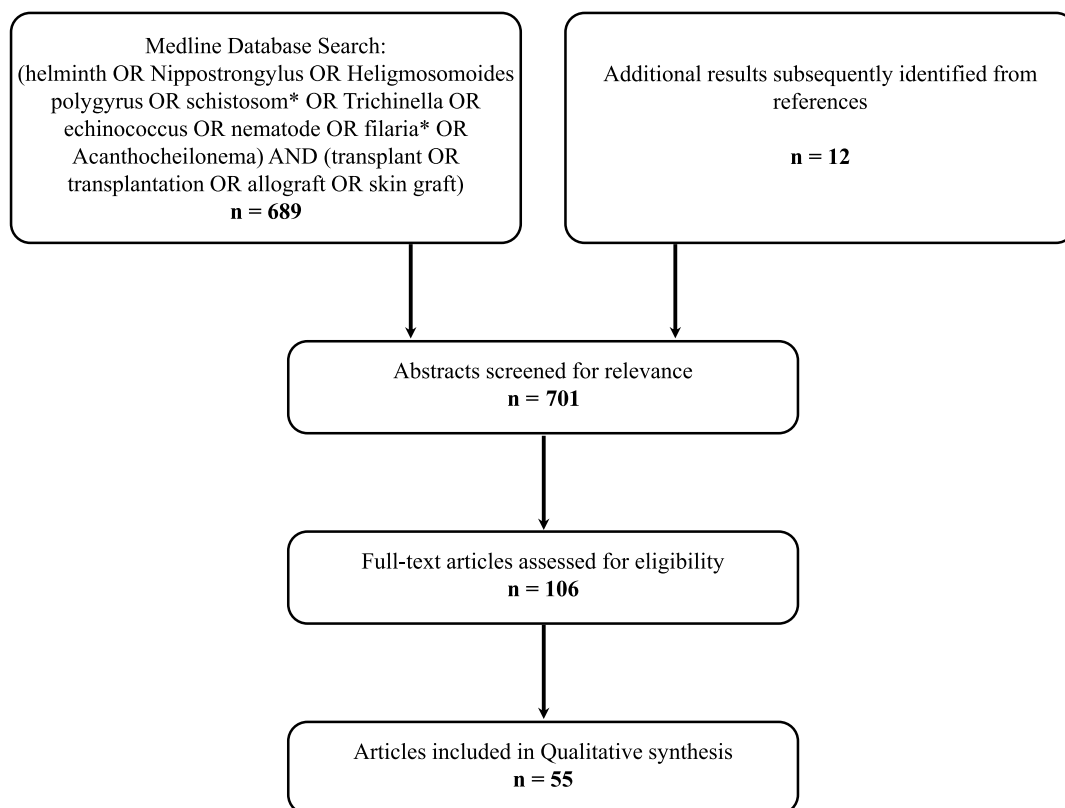


FIGURE 1. Search strategy.

been approved by the U.S. Food and Drug Administration and a number of multicenter randomized controlled trials have commenced (25). In the absence of a corresponding analysis of allograft survival in helminth infected hosts, we performed a publication search (Fig. 1) and report here a synthesis of the relevant literature.

***Echinococcus* Tapeworms**

The metacestode *Echinococcus multilocularis* (*Em*) is endemic among foxes in many parts of Europe and China such that humans can be affected as accidental hosts. Infection can result in severe disease with a clinical course resembling that of a malignant primary liver tumor (hepatocellular carcinoma) (26). Radical surgical resection of liver lesions has been shown to be effective in improving survival and orthotopic liver transplantation is now largely accepted as appropriate treatment for advanced disease (27). Disease progression caused by the parasite has been found to advance rapidly in the presence of host immunosuppression either as a result of medication (1, 28) or HIV infection (2, 29). This finding led to guidelines recommending reduced immunosuppression regimens after liver transplantation for *Em* (30) and long-term follow-up reported unexpectedly satisfactory tolerance of the allografts (3, 27). Tao et al. have subsequently corroborated this finding in an experimental rat model of liver transplantation with *Em* infection (3, 31) (Table 1). In this study, survival after orthotopic liver transplantation found to be significantly prolonged for *Em*-infected rats compared with naïve controls (15.5±3.9 vs. 9.9±2.3 days; $P<0.05$). The *Em*-infected group was also found

to have reduced CD4⁺, CD8⁺, and CD28⁺ T-cell populations in peripheral blood, raised serum interleukin (IL)-10 levels, and reduced histologic liver allograft rejection scores, all of which reached statistical significance ($P<0.05$) (4, 31). More recently, Hepiretihan et al. have shown that *Em* infection exerts a similar protective effect against rejection of rat heart allografts (16.2±3.2 vs. 7.9±1.9 days) (5, 32). This was associated with a reduction in graft-infiltrating CD8⁺ lymphocytes and a shift toward a Th2 cytokine profile in the serum of peripheral blood. In the clinical setting, eradication of *Em* infection usually proves impossible. It therefore remains as yet unclear as to whether graft protection is afforded by an ongoing influence of the parasite or as the result of a Th2 cytokine environment at the time of alloantigen presentation.

***Nippostrongylus* Roundworms**

Beneficial enhancement of allograft tolerance in the presence of helminth infection has now been demonstrated with a number of parasite species and does not seem to be restricted to specific organs or host species (Table 1). In 1996, Ledingham et al. demonstrated marked improvement in the survival of kidney allografts in rats infected with the gastrointestinal nematode, *Nippostrongylus brasiliensis* (*Nb*), or inoculated with its secretory products compared with naïve controls (32±10, 21±4.6, and 9.7±1.2 days, respectively; $P<0.001$) (6, 33). Representative histologic examination 5 days after transplantation showed a dramatic reduction of graft cellular infiltration in the *Nb*-infected group and this finding was supported quantitatively with flow cytometric analysis of digested allograft single-cell suspensions (84% and

81% reduction of CD8⁺ and CD4⁺ lymphocytes, respectively). Although the graft protection afforded by *Nippostrongylus* excretory-secretory products (NES) was less pronounced, the pharmacokinetic profile of the active mediator(s) in NES is unknown and this may therefore be a purely dose-dependent difference.

The same group later showed similar (2.8-fold) graft protection in a mouse cardiac allograft model (7, 34). *Nb* infection is known to induce a strong Th2 response in its host (8, 35), leading those authors to hypothesize that polarization away from Th1-mediated allograft rejection may afford allograft protection. *Nb* usually achieves only a limited infection in rodents—most mouse strains can clear the infection within 10 days of inoculation with third-stage larvae (1, 35). The finding that mouse heart allografts can survive for considerably longer than the period of infection (9, 34), presents the exciting therapeutic prospect that graft protection is afforded by T-cell “phenotype switching” at the time of alloantigen presentation rather than a mechanism dependent on persisting parasite infection. Enzyme-linked immunosorbent assay analysis of mixed lymphocyte reactions supports this hypothesis in demonstrating a Th2 cytokine profile (IL-4 and IL-6) in alloreactive lymphocytes from *Nb*-infected mice compared with naïve controls (34, 36).

Schistosome Flukes

Schistosoma is a genus of blood-borne trematode with a current prevalence of infection estimated at more than 200 million people worldwide (10, 37). In light of the very widespread prevalence of schistosomiasis and the diminishing supply of suitable cadaveric donor organs for transplantation, a number of human liver (11, 38, 39) and kidney (12, 40) transplants in patients with clinical schistosomiasis have been performed (donor and recipient, donor alone, and recipient alone). No attempts at reducing immunosuppression or analyzing differences in rejection rates have as yet been reported. However, one remarkable study has looked at the differential rejection of full-thickness skin grafts in Egyptian patients with established schistosomiasis compared with healthy volunteers. Aboul-Enein et al. (9, 41) recruited 19 patients with advanced *Schistosoma mansoni* infection and 16 parasite-free volunteer controls. Then, 2.5-cm-diameter full-thickness skin grafts were applied to the volar forearm. Two grafts were performed for each patient: one ABO-matched allograft from a noninfected donor and one autograft control. Grafts were assessed daily for signs for rejection and rejection was then confirmed histologically. The control group rejected their allografts after a mean of 10.06±3.21 days. Of the *Schistosoma*-infected patients, in 16 cases, rejection occurred after a mean of 22.25±6.46 days. The remaining three infected patients showed no signs of rejection 60 days after the grafting procedure. Notably, the HLA status of donors and recipients was unknown in this study; therefore, the three cases of long-term graft tolerance may well be the result of coincidental HLA matching. In spite of this significant caveat, the difference in rejection times between the two groups was highly significant ($P<0.001$) and therefore unlikely to be the result of differences in HLA matching alone.

Allograft protection with *Schistosoma* infection has previously been shown in a murine experimental model. In

1977, Araujo et al. found a highly significant difference in the rejection of fully allogeneic skin grafts in *S. mansoni*-infected versus naïve recipient mice (14, 42). No difference was found after 30 days of infection, but for grafts performed after 60 days of infection, infected recipients tolerated their grafts for an average of 50% longer than naïve controls. A strongly positive correlation between graft survival and the number of live parasites remaining in the recipient was also seen ($r=0.096$).

Trichinella

Finally, murine experimental models of other helminth species have also demonstrated enhanced tolerance of skin allografts. *Trichinella spiralis* is a small nematode that encysts in mammalian muscle and can affect humans who consume infected meat. Suppression of skin allograft rejection in mice infested with *Trichinella* was first described by Svet-Moldavsky et al. in 1969 (15, 43) and subsequently confirmed by Faubert and Tanner (16, 44) and Chimyshkyan et al. (18, 45). In 1995, Alkarmi et al. performed fully allogeneic skin grafts (C57BL/6 to BALB/c recipients and vice versa) on multiple groups of mice at varying time points after infection (17, 46). Graft protection was found to be critically dependent on the timing of skin transplantation in relation to initial infection and a maximum effect of 3.5-fold prolongation of graft survival was found when the transplants were performed 3 days after initial infection. Repeated intraperitoneal injection of parasite secretions (culture supernatants) replicated the effect of active infection in a dose-dependent fashion with an observed maximum twofold prolongation in graft survival (18, 46).

Evolution of Regulation

Coevolution of helminths and humans over millions of years (19, 47) has resulted in multiple effective mechanisms of immunomodulation, which may individually or in combination be responsible for the prolongation of allograft survival. Certainly, it is now clear that helminths act via multiple distinct and synergistic pathways to down-regulate host immunity. Expansion of Treg populations in response to helminth infections such as *Heligmosomoides polygyrus* (20, 48) and *S. mansoni* (21, 49) is one well-recognized mechanism, but the same parasites can also engender immunosuppressive activity in B-cell populations as well as modified dendritic cell and macrophage populations (21, 22).

In this context, it is possible that therapeutic extension of graft survival would also require more than one particular immunomodulatory pathway. With respect to Treg expansion, exogenous IL-2:anti-IL-2 antibody complex is a potent short-term stimulant of Treg populations, which can effect long-term tolerance of allogeneic islet grafts in the absence of immunosuppression (22, 50). However, multiple attempts to achieve similar tolerance of allogeneic skin grafts (BALB/c to C57BL/6) have failed (23, 51). It is well known in the experimental and clinical setting that tolerance of skin allografts presents a particular challenge (compared with the solid-organ transplants of heart, liver, or kidney). Important factors to overcome are likely to be the large proportion of resident dendritic cells in skin (24, 51) and more potent Toll-like receptor stimulation by colonizing microbes (25, 52). Failure of IL-2:anti-IL-2 complexes to achieve the same level of protection of fully allogeneic skin grafts against rejection (26, 51) that is seen in *Schistosoma* infection (27, 41) strongly

suggests that Treg-independent mechanisms also play a critical role in helminth-derived allograft protection.

CONCLUSIONS

Enhanced allograft tolerance with helminth infection has now been demonstrated in multiple species across multiple organ allograft models (mouse heart and skin; rat heart, liver, and kidney). These experimental data are consistent with historical results of skin grafting in established human schistosomiasis and supported by more recent anecdotal suggestions of reduced immunosuppression requirement after liver transplantation for human *Echinococcus* infection (27). Thus, the possibility can now be entertained of including specific live (nonpathogenic) helminth infection, or defined products from immunoregulatory helminths, in future transplantation protocols. Ongoing trials of live *T. suis* therapy in inflammatory bowel disease (25) are keenly awaited as potential path-finding studies for translation of this concept to the clinic.

There are indeed multiple potential opportunities for helminthic and helminth product therapy in transplantation. The most promising is with living-donor transplantation, whereupon a course of helminthic therapy may be commenced before the time of transplantation, allowing alloantigen presentation to occur in a tolerogenic environment (either at the time of the transplantation itself or with known defined alloantigens beforehand). Although treatment with active helminth infection has been shown to be a safe therapeutic approach (25), reports of mild gastrointestinal side effects do exist and might limit patient acceptability (53). Identification and synthetic production of the active compounds within helminthic secretions for novel pharmaceutical intervention is a definitive goal and the focus of much attention (54). Measured against current transplant immunosuppression regimens with multiple serious adverse effects and inadequate long-term organ protection against rejection, therapy with helminths or their products presents the exciting opportunity of a safe, effective, and long-overdue alternative.

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